

Department of Gastroenterology

Helsinki University Hospital

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University of Helsinki

Helsinki, Finland 2019

Autoimmune hepatitis: Epidemiology, prognosis and follow-up

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Academic dissertation

To be presented for public discussion with the permission of the Faculty of Medicine of the University of Helsinki, in Lecture hall 1, Biomedicum, on the 10th of May, 2019 at 11 o'clock.

This dissertation has been made in participation with the Doctoral Programme in Clinical Research

The Faculty of Medicine uses the Urkund system (plagiarism recognition) to examine all doctoral dissertations.

Englannin kielen tarkistus Luanne Siliämaa.

ISBN 978-951-51-5134-6 (Print)

ISBN 978-951-51-5135-3 (Online)

ISSN 2342-3161 (Print)

ISSN 2342-317X (Online)

Helsinki, Finland 2019

Kirjapaino Unigrafia

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To Niina, Eino and Otto

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This thesis is based on the following original articles referred to in the text by their Roman numerals.

- I** Puustinen Lauri, Barner-Rasmussen Nina, Pukkala Eero, Färkkilä Martti. Incidence, Prevalence, and Patient Survival of Autoimmune Hepatitis between 1995 and 2015: A Nationwide Register-Based Cohort Study in Finland. *Dig Liver Dis* 2019 Epub ahead of print.

- II** Puustinen Lauri, Boyd Sonja, Mustonen Harri, Arkkila Perttu, Arola Johanna, Färkkilä Martti. Prognostic value of clinical variables and liver histology for development of fibrosis and cirrhosis in autoimmune hepatitis. *Scand J Gastroenterol* 2017;52:321-327.

- III** Puustinen Lauri, Hakkarainen Antti, Kivisaari Reetta, Boyd Sonja, Nieminen Urpo, Färkkilä Martti, Lundbom Nina, Arkkila Perttu. ³¹Phosphorus magnetic resonance spectroscopy of the liver for evaluating inflammation and fibrosis in autoimmune hepatitis. *Scand J Gastroenterol* 2017;52:886-892.

- IV** Puustinen Lauri, Boyd Sonja, Arkkila Perttu, Isoniemi Helena, Arola Johanna, Färkkilä Martti. Histologic surveillance after liver transplantation due to autoimmune hepatitis. *Clin Transplant* 2017;31:e12936.

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*) I, Elsevier; II, III, Taylor & Francis; IV, Wiley publishing

Abbreviations

AC	Anabolic charge
AIH	Autoimmune hepatitis
ALP	Alkaline phosphatase
ANA	Anti-nuclear antibodies
CI	Confidence interval
CTLA4	Cytotoxic T lymphocyte antigen 4
EASL	The European Association for the Study of the Liver
GPE	Glyserophosphoethanolamine
HILMO	Hospital discharge registry
HUH	Helsinki University Hospital
IAIHG	The International Autoimmune Hepatitis Group
ICD-10	International Classification of Diseases and Related Health Problems volume 10
LFT	Liver function tests
LKM	Liver-kidney-microsome
LT	Liver transplantation
MRI	Magnetic resonance imaging
NA	Not available
NPV	Negative predictive value
NS	Statistically not significant
OR	Odds ratio
pANCA	Perinuclear anti-neutrophil cytoplasmic antibodies
PBC	Primary biliary cholangitis

PDE	Phosphodiester
PE	Phosphoethanolamine
PEP	Phosphoenolpyruvate
PIC	Personal identity code
PME	Phosphomonoester
³¹ P MRS	³¹ Phosphorus magnetic resonance spectroscopy
PPV	Positive predictive value
PSC	Primary sclerosing cholangitis
SII	The Social Insurance Institution of Finland
SLA	Soluble liver antigen
SMA	Smooth muscle antibodies
SMR	Standardised mortality ratio
TE	Transient elastography (Fibroscan)
TNF	Tumour necrosis factor

Abstract

Aims: This thesis includes one study (**Study I**) focused on epidemiological data regarding autoimmune hepatitis (AIH) and three studies (**Studies II-IV**) on follow-up of AIH. The aims were to assess the incidence, prevalence, and causes of death in patients with AIH. Three other studies aimed to determine the role of follow-up liver biopsies in patient surveillance, to study non-invasive methods to quantify inflammation and fibrosis in AIH, and to evaluate the prognosis of patients with AIH after liver transplantation.

Patients and methods: Patients with AIH code K73.2 or K75.4 with special reimbursement in the Social Insurance Institution of Finland registry were cross-referenced with the data from the hospital discharge register to validate diagnoses. Five controls for all AIH patients were identified from Statistics Finland. Data from the Finnish cancer register were used to calculate standardized mortality ratios (**Study I**). All patients with AIH diagnosis in Helsinki University Hospital were included in the retrospective study of the impact of liver histology on disease progression, with special emphasis on follow-up biopsies (**Study II**). Twelve patients with AIH were investigated with magnetic resonance spectroscopy, liver biopsy, and transient elastography (**Study III**). Follow-up biopsies of all Finnish liver transplant recipients with AIH as an indication for transplantation were combined with clinical data to evaluate the prognosis and risk factors for AIH recurrence and graft loss (**Study IV**).

Results: We showed that the median AIH incidence between 1995 and 2015 was 1.0/100,000/year (1.2/100,000/year in women and 0.38/100,000/year in men) and increased from 0.28/100,000 to 1.0/100,000 during the study period. The prevalence of AIH in 2015 was 14/100,000, 23/100,000 in women and 6.6/100,000 in men). The standardised mortality ratio was increased in all age groups and both genders. The most prevalent excessive causes of mortality when compared to the standard population were hepatocellular carcinoma, liver cirrhosis, and AIH per se (**Study I**).

We identified the following prognostic variables for advancing fibrosis or cirrhosis in follow-up biopsies: interface or total inflammation, necrosis, cholestasis, or rosette formation in the baseline biopsy. If inflammation in the follow-up biopsies

was constantly grade two or more in the Metavir scale, the hazard ratio (HR) for cirrhosis was 5.1, (95 % Confidence interval (CI) 1.6-16.2), $p < .005$). If interphase inflammation was constantly grade two or more, the HR was 6.1 (95 % CI 1.9-20.2), $p < .005$. Only 7% of patients were cirrhotic at baseline. Fibrosis progressed in 42% of patients, remained stable in 39% and resolved in 18% **(Study II)**.

When compared to liver histology, magnetic resonance spectroscopy revealed distinctive ratios of selected hepatocyte metabolites in patients with advanced fibrosis or active inflammation in 12 consecutive AIH patients. Transient elastography was ineffective in fibrosis quantification **(Study III)**.

After liver transplantation, AIH recurred in 36% of patients; the median time until recurrence was 5 years (range 1.1-15 years). Recurrent AIH did not affect patient or graft survival. Patient and graft survival were 94% and 86% at 1 year, 86% and 91% at 5 years, and 77% and 74% at 10 years, respectively. Immunosuppression without mycophenolate mofetil or azathioprine increased the risk of AIH recurrence. Recurrence was less common in patients without overlapping cholangitis **(Study IV)**.

Conclusions: The incidence and prevalence of AIH is similar in Finland as reported in other countries. Female preponderance is notable. We demonstrate that, especially in women, AIH occurs at all ages and often in the elderly. Hepatocellular carcinoma is rare but statistically is the most important cause of excess death. While liver biopsies might play a role in the follow-up of AIH, there are currently no good prognostic models that encompass liver histology. Ongoing histological inflammation is a risk factor for fibrosis progression and development of cirrhosis. Magnetic resonance imaging of the liver is a promising follow-up tool and is acceptable to patients. Transient elastography was not useful in this setting. AIH recurs after liver transplantation in 36% of patients but is of primarily benign disease course. If tolerated, use of an antimetabolite is advisable after liver transplantation.

1 Introduction

Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease, characterised by interface hepatitis on histologic examination, hypergammaglobulinemia and autoantibodies measured from the blood ¹. The aetiology of autoimmune hepatitis is mostly unclear, but a triad of environmental triggers, failure in the immune tolerance and susceptibility due to genetic factors, induce a T-cell mediated immune attack against liver antigens leading to necroinflammatory hepatocyte damage and fibrosis generation ^{2,3}. Although up to 25% of AIH present with an acute onset of disease ⁴, AIH is generally considered as a chronic disease in which inflammation leads to fibrosis and cirrhosis ⁵, and it seems that advanced liver disease per se is important for patient outcome ⁶⁻¹¹. Studies on effective treatment options have been reported as early as in the 1970s and 1980s, and our treatment protocols are still based on these studies ^{12,13}. The incidence and prevalence of AIH is estimated to be equal to primary biliary cholangitis and twice the amount of primary sclerosing cholangitis ⁵. Epidemiological data of AIH are scarce. Also, there are no epidemiological data of AIH in Finland. Clinical decisions regarding the treatment of AIH should be based on knowledge of the epidemiology and the prognosis of this disease.

Liver histology is needed in AIH to establish diagnosis ^{14,15}, and histological findings are known to be of prognostic importance ^{9,10,16-18}. In Helsinki, we have taken routine follow-up liver biopsies and will determine their impact on treatment choices and prognosis. Furthermore, in HUS Medical Imaging Center, MRI spectroscopy with 3 Tesla imaging modality has been used in non-alcoholic fatty liver disease ¹⁹ to evaluate fibrosis and could also be used in AIH patients. Transient elastography (Fibroscan) is an ultrasound-based technic which assesses fibrosis in liver disease ^{20,21}. Transient elastography can distinguish advanced fibrosis and cirrhosis from normal liver histology but does not reliably show mild fibrosis. It also plays no role in evaluation of inflammation. New non-invasive tests in evaluation of inflammation and fibrosis are needed, and we hypothesise that MRI could be useful in this setting. In this study, liver histology served as the gold standard in determining the fibrosis stage and inflammation grade.

AIH is a well-established indication for liver transplantation (LT) in cirrhotic patients with untreatable symptoms of portal hypertension, poor liver function or general symptoms ⁵. In Helsinki University Hospital (which performs and follows up all Finnish LT patients), we have a comprehensive registry of liver transplanted AIH patients. Their prognosis after transplantation was evaluated within this study. In addition, these patients undergo regular protocol liver biopsies after transplantation, and the reoccurrence of AIH after transplantation will be evaluated. During 1982-2008, of the 667 liver transplantations performed in Finland, 42 (6%) were done because of AIH ²².

2 Review of the literature

2.1 Epidemiology of AIH

AIH is a rare and usually chronic liver disease. Incidence rates from 0.7 to 2.0 per 100,000 person-years have been reported previously, depending on the population and data collecting method. The point prevalence rate has been reported from 8.0 to 43 per 100,000 person-years^{7,23-30}. There is variation regarding how the data is gathered in the studies, and only one of the previous studies included a complete nationwide registry⁷. The highest prevalence rate of 43 per 100,000 was reported in Alaska²⁶, whereas the prevalence in Southern Israel and Sweden were only 8.0 and 10.7 per 100,000^{24,30}. In Alaska, patients also had a more severe presentation than what has been reported elsewhere²⁶. It has been speculated, that ethnic stability and background may play a role in the epidemiology of AIH, but the longest observation period published so far (from Denmark 1994-2012)⁷, showed that the incidence of AIH nearly doubled from 1.37 to 2.33 per 100,000 person-years. Incidence rose both in women and men. It remains to be seen whether this is due to improved diagnostics, or to a true increase in incidence. Altogether, this finding implies that the incidence has risen in a genetically quite stable population.

The most stable finding in published studies is that AIH is more common in women. The women to men ratio in studies in general has been roughly three to one. The highest women to men ratio was reported in the Valencia district in Spain²⁸, with eighteen to one. Older studies have shown a bimodal distribution of incidence according to age, with peaks after puberty and around fifty years of age^{23,26,30-32}. This finding has been challenged in more recent, and more comprehensive studies^{7,29}. It is important to recognise that AIH can occur in all ages and both genders. Results from previous epidemiological studies are illustrated in Table 1.

TABLE 1. Incidence and prevalence rates of autoimmune hepatitis in selected registries, from **Study I**, with permission from Elsevier

<u>Location</u>	Incidence	Prevalence	<u>Period</u>	<u>Population</u>	<u>Reference</u>
	/100,000	/100,000			
Oslo, Norway	1.9	16.9	1986-1995	130,000	²³
Canberra, Australia	NA	8	NA	525,000	²⁵
Southern Israel	0.7	11.0	1995-2010	910,000	²⁴
Alaska	NA	42.9	1984-2000	100,312	²⁶
Denmark	1.7	23.9	1994–2012	5,600,000	⁷
	Women 2.4	34.6			
	Men 0.9	13.0			
Valencia, Spain	0.8	11.6	1990-2003	112,003	³³
	Women 1.4	Women 19.2			
	Men 0.3	Men 3.7			
Valencia, Spain	1.1	NA	2003	1,774,736	²⁸
	Women 2.0				
	Men 0.1				
Canterbury, New Zealand	2.0	24.5	2001-2008	494,170	²⁷
	Women 35.3				
	Men 13.2				
Sweden	0.9	10.7	1990-2003	715,000	³⁰
	Women 1.2	15			
	Men 0.5	6.2			
Amsterdam, The Netherlands	1.1	18.3	1967-2011	799,000	²⁹

NA, Not available

2.2 Aetiology and pathogenesis of AIH

AIH may be a group of heterogeneous diseases, with commonly agreed diagnostic criteria, Table 2 and 3. Diagnosis of AIH is based on the detection of autoantibodies, hypergammaglobulinemia, and chronic inflammation, preferably interface hepatitis, shown in the liver biopsy ³⁴. The aetiology of AIH is complex and largely unknown. The current opinion is that in a genetically susceptible person, a triggering antigen can induce an unfavourable immune response and a break-down in immune tolerance ^{2,35-37}. The triggering epitope is probably a short epitope in an infectious or toxic agent. Homology between this epitope and self-antigens may stimulate a cross-reactive humoral and/or cellular immunological response, sensitising immunocytes to extend the immunological reaction beyond precise exoantigens. Immune environment in AIH patients is presumably favourable to prolonged and extended immune reactions and is thought to be different in different geographical regions and ethnic groups ⁵.

Multiple triggering factors have been proposed: Viruses include hepatitis A ³⁸, hepatitis B ³⁹, hepatitis C ⁴⁰, measles ⁴¹, and Epstein-Barr virus ⁴². Drugs that have been reported include nitrofurantoin ⁴³, minocycline ⁴⁴, atorvastatin ⁴⁵, methyldopa and hydralazine ⁴⁶. However, the lag time between a triggering agent and the onset of the clinical manifestations of the disease may be long, and usually a triggering agent cannot be identified, or there may not be one.

AIH is a heterogeneous disease. Altogether, genome-wide association study was performed in patients from the Netherlands and Germany in 2014 ⁴⁷. The study identified risk alleles in the major histocompatibility complex region and identified variants of SH2B3 and CARD10 as likely risk factors. The conclusion of the authors was that the genetic basis for AIH is complex. It can be assumed that different genetic traits are risk factors or even causes for their own type of AIH, but in a large cohort in a heterogeneous mixture of disease phenotypes, these genes fade out in the analysis.

Molecular mimicry of a foreign and a self-antigen is a common hypothesis for loss of self-tolerance, but this mechanism has not been established in AIH ⁴⁸. Genetic factors influence antigen presentation and CD4+ helper T cell recognition. In

genetic studies, it has been shown that susceptibility alleles of AIH in Caucasians reside in the DRB1 gene in the class II major histocompatibility complex and are DRB1*0301 and DRB1*0401^{1,49}. Polymorphisms of the tumour necrosis factor (TNF) – α gene and cytotoxic T lymphocyte antigen 4 (CTLA4) gene⁵⁰ –have been identified in Caucasian AIH patients, and TNF- α is a known potent immunoactivator, as CTLA4 is a crucial regulator of self-tolerance.

2.3 Clinical spectrum and diagnosis of AIH

The clinical spectrum of AIH is wide. Patients can be asymptomatic individuals with elevation of liver enzymes. On the other end of the spectrum is a fulminant life-threatening hepatitis. Patients can have symptoms due to hepatic or systemic inflammation, complications of cirrhosis, or even in extrahepatic organs, such as joints, skin, muscles or the gastrointestinal tract ^{5,51}.

Diagnosis of AIH is based on the detection of autoantibodies, hypergammaglobulinemia, and chronic inflammation, preferably interface hepatitis, shown in the liver biopsy ³⁴. The International Autoimmune Hepatitis Group (IAIHG) have released their recommendations of diagnostic scoring in 1999 (Revised scoring system for diagnosis of autoimmune hepatitis), which are suitable for clinical use, as well as investigational purposes, Table 2 ¹⁴. Newer and simpler diagnostic criteria were published in 2008: Simplified scoring criteria for the diagnosis of autoimmune hepatitis ¹⁵ showed similar performance with fewer parameters, Table 3. Both scoring systems have their advantages ⁵²: 1999 criteria have twelve parameters and are more sensitive, while 2008 has four parameters with better specificity and predictability. Also, 1999 criteria perform better in AIH with atypical features, and 2008 criteria are better in excluding patients with non-immune mediated liver diseases with nonspecific immunological alterations. There seems to be no difference in the validity of diagnosis or treatment response between probable and definite diagnosis, which concerns both diagnostic criteria ⁵³.

Table 2.Revised scoring system for diagnosis of autoimmune hepatitis(adapted)¹⁴

Variable	Points
Female sex	+2
Alkaline phosphatase to aspartate transferase ratio	
<1.5	+2
1.5-3.0	0
>3.0	-2
Serum globulins or immunoglobulin G above normal	
>2	+3
1.5-2.0	+2
1.0-1.5	+1
<1.0	0
Antinuclear, smooth muscle or liver-kidney microsome antibodies	
>1:80	+3
1:80	+2
1:40	+1
<1:40	0
Anti-mitochondrial antibodies	-4
Viral hepatitis positive	-3
Viral hepatitis negative	+3
Drug history positive	-4
Drug history negative	+1
Alcohol <25 grams daily	+2
Alcohol >60 grams daily	-2
Interface hepatitis	+3
Lymphoplasmacytic infiltrate	+1
Rosettes	+1
None of the above	-5
Biliary changes	-5
Other changes	-3
Other autoimmune diseases	+2
Positive for other defined antibodies (optional)	+2
Human leucocyte antigen DR3 or DR4 (optional)	+1
Response to therapy	+2
Relapse after therapy withdrawal	+3
	Sum
Pre-treatment definite AIH	>15
Pre-treatment probable AIH	10-15
Post-treatment definite AIH	>17
Post-treatment probable AIH	12-17

Table 3. Simplified Scoring System for Diagnosis of Autoimmune Hepatitis
(adapted) ¹⁵

Variable	Points
Antinuclear or smooth muscle antibodies 1:40	1
Antinuclear or smooth muscle antibodies $\geq 1:80$ or Antibodies to liver-kidney microsome or Antibodies to soluble liver antigen	2
Immunoglobulin G > upper limit of normal	1
Immunoglobulin G > 1.1 times upper limit of normal	2
Compatible histology	1
Typical histology	2
Absence of viral hepatitis	2
	Sum
Definite diagnosis	≥ 7
Probable diagnosis	6

2.4 Classification of AIH types

Traditionally, AIH has been divided into types 1 and 2, Table 4. In 2000, a type 3 AIH was proposed ⁵⁴, however, some experts see type 3 AIH as a subtype of type 1 autoimmune hepatitis⁵¹. Soluble liver antigen (SLA)-1 ⁵⁵ was shown to be present in the sera of patients with unknown inflammatory hepatitis. It has now been shown to be a strong predictor of relapse after treatment withdrawal ⁵⁶. Some experts see this antigen as a marker of type 3 AIH ⁵, while some investigators see this as a variant of type 1 AIH. Some patients lack characteristic autoantibodies ⁵⁷ even if they have an established AIH diagnosis.

Type 1 is typically characterised by the expression of smooth muscle (SMA) ⁵⁸ or anti-nuclear antibodies (ANA) ⁵⁹, or both. Atypical perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) ⁶⁰ are present in as many as 96% of type 1 AIH patients but should be absent in type 2 patients. Type 2 patients are positive for the liver-kidney-microsome (LKM) antibody -1⁶¹. It was first recognised in children aged 2-14 years old but has since been shown to also occur in adults ⁶². Target antigens in liver of type 1 patients are yet to be characterised, but LKM-1 in type two has a target antigen cytochrome P450 2D6 expressed in the liver ⁶³. This antigen is also homologous to the hepatitis C genome, as well as the cytomegalovirus and herpes simplex virus, supporting the hypothesis that viral infections may be the cause of AIH ⁶⁴.

Table 4. Traditional classification of AIH

Feature	Autoimmune hepatitis type 1	Autoimmune hepatitis type 2
Autoantibodies	Anti-nuclear, smooth-muscle, and perinuclear anti-neutrophil antibodies, and soluble liver antigen	Liver-kidney microsomal antibody
Age	Any age	Children and adolescents
Association to HLA haplotypes	DR3, DR4	DR3
Clinical severity	Variable	Severe
Treatment failure	Uncommon	Frequent
Need for long-term maintenance therapy	Variable	Approx. 100%

2.5 Accompanying cholangitis in patients with AIH

Patients with primary biliary cholangitis (PBC) may have autoimmune hepatitis ⁶⁵, as may patients with primary sclerosing cholangitis (PSC) ⁶⁶, the latter known to be highly prevalent in children ⁶⁷, and patients with inflammatory bowel disease ⁵⁷. The 2011 position statement by The International Autoimmune Hepatitis Group (IAIHG) proposes that these patients should be categorised according to their predominant feature as AIH, PBC or PSC ⁶⁸. That same paper also states that the number of patients with these formerly called overlap syndromes, is probably not sufficient enough to enable clinical studies. In our studies, we have decided to include patients who fulfil the Simplified criteria for the diagnosis of autoimmune hepatitis ¹⁵ and to report whether these patients had an accompanying autoimmune cholestatic disease. The transplantation rate was higher in children with AIH and PSC (87%) compared to pure AIH (77%)⁶⁹. In adults, AIH+PSC patients had a transplantation free survival of 67% versus patients with pure AIH (92%)⁷⁰. AIH+PBC has not been shown to affect patient survival, and they respond to corticosteroid treatment similarly as pure AIH patients (75% vs. 64%)⁷⁰.

2.6 Treatment of AIH

The European Association for the Study of the Liver clinical practice guidelines from 2015 (EASL) recommend all patients with AIH should be treated ⁷¹. The goal of the treatment is to treat symptoms of the liver disease and prevent progression of liver damage to cirrhosis by suppressing inflammatory activity. The American Association for the Study of the Liver Disease practice guidelines from 2010 stated that symptomatic patients or patients with necrotic inflammation or high liver function tests should be treated, whereas in other patients the option to treat should be individualised ⁵¹. There is uncertainty regarding treating patients with only mild inflammatory activity since we have only one study which retrospectively compared untreated and treated patients with mild activity with no symptoms ⁷², and they only had follow-up data of eight patients with mixed results. They still showed that this patient population exists, and the total number of untreated patients was 21 (7%).

The basis of treatment has been corticosteroids alone or in combination with azathioprine ⁷³. Second line treatment options for corticosteroid or azathioprine intolerant patients include 6-mercaptopurine ⁷⁴, mycophenolate mofetil ⁷⁵, budesonide ⁷⁶, of which budesonide is the only one tested in a randomised trial. Treatment options for steroid-refractory AIH include cyclosporine ⁷⁷, tacrolimus ⁷⁸, rituximab ⁷⁹ and infliximab ⁸⁰. These are included in the AASLD ⁵¹ guidelines but are based on case reports or case series. And if all this fails, liver transplantation is a viable option with a 74 percent 10-year patient and 85 percent graft survival ²².

2.7. Follow-up of AIH patients

The ideal endpoint of initial therapy is normalisation of transaminases, immunoglobulin G, and resolution of tissue damage shown by liver biopsy, which is achievable in 90% of patients ⁵¹. Even in remission prior to therapy withdrawal, 60% of patients still relapse ⁸¹. Liver biopsy prior to treatment tapering is essential, since up to 55% percent of patients with normal transaminases still

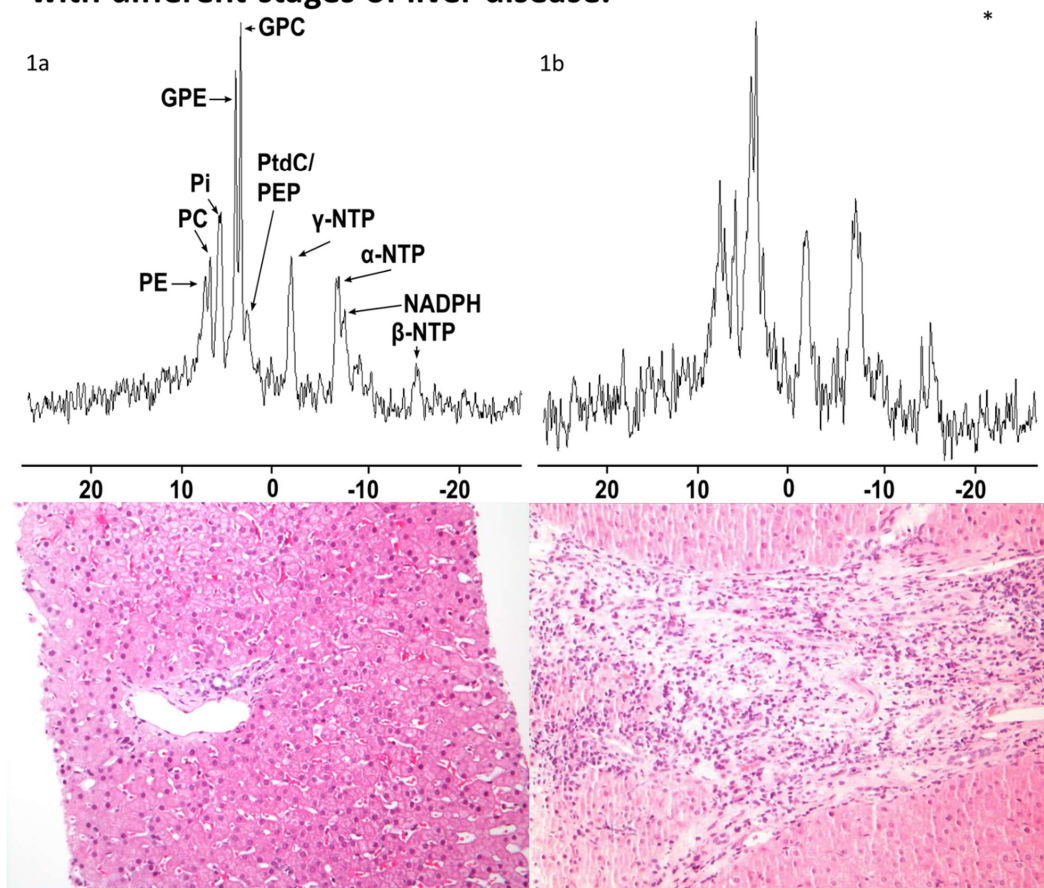
have interface inflammation in the liver ⁸², and these patients likely relapse after treatment discontinuation ⁵¹, even though this subject is poorly studied. Both EASL and AASLD recommend treatment tapering after two years of remission ^{51,71}.

Follow-up imaging is not routinely necessary in AIH patients. Cirrhotic AIH patients have a 0.2% annual risk of developing hepatocellular carcinoma (HCC) ⁸³, and HCC surveillance is unlikely cost-effective until models to predict high risk HCC patients are developed. It is advisable that patients with elevated alkaline phosphatases during follow-up undergo cholangiography to detect possible associated cholangitis.

³¹P Phosphorus magnetic resonance spectroscopy (³¹P MRS) has been evaluated in hepatitis c and non-alcoholic fatty liver disease ^{19,84} and has shown promising results. ³¹P MRS can show both inflammation and fibrosis, which would be ideal in AIH follow-up. Anabolic charge (AC) is combination of elevated total phosphomonoester (PME) and decreased total phosphomonoester (PDE) in a fibrotic liver. Measuring anabolic charge can quantify fibrosis and separate patients with no or mild fibrosis from patients with advanced fibrosis ^{85,86}. Phosphoethanolamine (PE) is a compound within the PME peak, and glyserophosphoethanolamine (GPE) is a part of PDE peak within the ³¹P MRS spectrum. Phosphoenolpyruvate (PEP) is a link in hepatic gluconeogenesis but its role in liver injury is unknown ⁸⁷. Two ³¹P MRS spectra examples are illustrated in Figure 1.

Transient elastography (TE) has been evaluated in AIH patients in two series comprising 28 patients but these series also included other liver diseases such as viral hepatitis. The authors reported only pooled results and showed that TE was able to reliably separate patients with a Metavir⁸⁸ score <2 from a Metavir score ≥ 2 patients ^{89,90}. On the other hand, published case reports of AIH patients have shown disproportionally high TE results, presumably by ongoing inflammation ^{20,91}. In these cases, elasticity levels normalised after AIH treatment initiation.

Figure 1. Illustrative spectra and histology of two AIH patients with different stages of liver disease.



1a) Normal histology and corresponding ^{31}P MRS spectrum

1b) G3F1 liver histology with interphase hepatitis and corresponding ^{31}P MRS spectrum

*Amplitudes (peak heights) have been normalised using GPC as a reference amplitude.

PE, Phosphoethanolamine ; PC, Phosphocholine; Pi, Phosphorus; GPE, Glycerophosphoethanolamine; GPC, Glycerophosphocholine; PtdC/PEP, Phosphatidylcholine/phosphoenolpyruvate; NTP, Nucleotide triphosphate, NADPH, Nicotinamide adenine dinucleotide phosphate; G2P2, Grade 2 and stage 2

From **Study III**, with permission ⁹².

2.8 Prognosis of AIH patients

The most significant predictor of poor outcome in AIH is cirrhosis at time of diagnosis. The presence of cirrhosis drops the 10-year survival from 94.0-94.4% to 61.9-61.7% ^{10,93}. Bridging necrosis predicts the development of cirrhosis ¹⁶, but there is no direct evidence that necrosis itself leads to impaired prognosis. In a European population of 103 patients ⁹⁴, where 29.1% of patients had cirrhosis at diagnosis, there was no statistical difference in prognosis between the groups with or without cirrhosis. In addition to a favourable outcome also in cirrhotic patients, cirrhotic patients seem to respond to treatment as positively as non-cirrhotic patients ⁹⁵. The impact of cirrhosis may also be mixed by the fact, that cirrhosis in AIH seems to be reversible ¹⁸: Nine out of fourteen patients showed resolution of cirrhosis in paired liver biopsies at diagnosis and after treatment initiation. Whether advanced fibrosis without cirrhosis affects survival, has not been studied.

EASL and AASLD recommend histological follow-up during maintenance therapy to confirm treatment response, but there is no data to show how histological findings during follow-up influence the outcome ^{5,51}. Liver biopsy is considered safe⁹⁶. Complications (including pain) are extremely rare (0.06-0.32% of patients) and 0.009-0.12% people die.

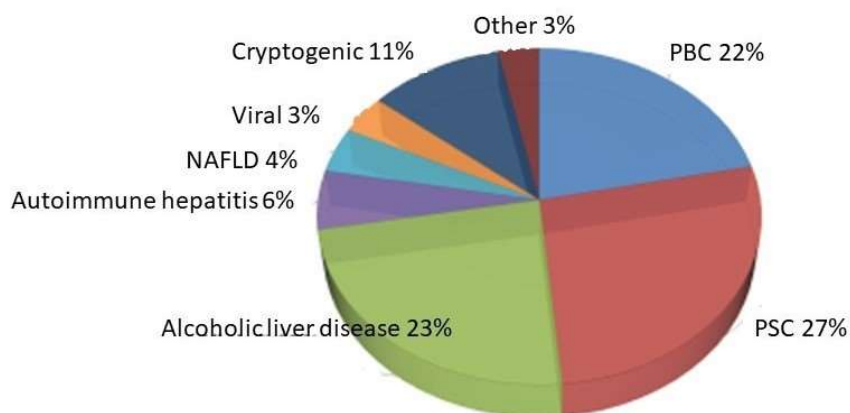
Most data that evaluate prognosis is focussed in baseline histology. Other, non-histological variables have been proposed: Non-white ethnicity ⁹⁷ and female sex ⁹⁸ have been shown to predict a poorer outcome, but these findings have not been confirmed in other studies. Not surprisingly, high liver function test levels and severe liver failure predict a poorer outcome ⁹⁹. Recurrent relapses also reduce survival ⁸¹.

2.9. Liver transplantation due to autoimmune hepatitis

Indications for liver transplantation (LT) due to autoimmune hepatitis (AIH) are identical to those with other liver diseases ¹⁰⁰. The most important causes are acute or subacute liver failure, decompensated cirrhosis, and hepatocellular cancer. Short-term prognosis after LT is good, with 90% one-year survival and 70% five-years survival ¹⁰¹, similar to alcoholic cirrhosis, but inferior to primary biliary cholangitis (PBC) ¹⁰². In the 2010 European Liver Transplantation registry data analysis, fatal infections occurred in the post-operative period at an increased rate in patients with AIH (HR 1.8, CI=1.2-2.6, p=.002 with PBC as the reference) ¹⁰², presumably due to the higher burden of immunosuppressive medication. The most worrisome finding in this report was that in AIH patients aged 50 or more, five-year survival was only 61% (confidence interval 51-70%). This should be taken into consideration in the pre-transplantation treatment of AIH patients, and it also highlights the importance of proper patient selection. Another typical feature of AIH as a LT indication is the high rate of recurrence in the graft (11%-40%) ¹⁰³⁻¹⁰⁵. Still, only 0.7% eventually die due to AIH recurrence ¹⁰⁶. A single centre report from the United Kingdom reported that overall graft loss was more frequent in AIH patients compared to PBC patients, HR 4.1 (95% CI 1.3–12.6) for recurrent disease and 1.6 (95% CI 1.2–2.) for overall graft loss ¹⁰⁷. Recipient HLA genotypes DR B1*0301 or DRB1*0401 ¹⁰⁸, high or poorly controlled necroinflammatory disease activity in the explant liver ¹⁰⁹, and concomitant autoimmune diseases and high aminotransferase and immunoglobulin G levels prior to LT ^{110,111} have been suggested as risk factors for AIH recurrence, but otherwise risk factors have been poorly defined. Acute rejection is more common in AIH patients than in LT patients in general ¹¹². It also seems that chronic rejection is more common in AIH patients ¹¹³. On the other hand, there is no evidence that acute or chronic rejections lead to recurrent AIH development or vice versa. Immunosuppressive treatment after LT due to AIH is similar to immunosuppression in other LT patients. Cyclosporine and tacrolimus are equally effective in these patients ¹¹⁰. Rapid tapering of steroids is a risk factor for disease recurrence ¹⁰⁹ and long-term corticosteroid therapy is safe and effective in these patients, resulting in a five-year AIH recurrence rate of 6% and a ten-year rate of

10% ¹¹⁴, Long-term corticosteroid use does not seem to result in excess osteoporosis or infection rate ¹¹⁴.

Figure 2. Primary chronic liver diseases leading to LT in Finland from 1982 to October 2018 (Finnish transplantation registry)



NALFD, Non-alcoholic fatty liver disease; PBC, Primary biliary cholangitis;

PSC, Primary sclerosing cholangitis

3 Aims of the Study

The aims of the study are to

Study epidemiology, prognosis and follow-up of AIH in Finland.

1. Examine the epidemiology and causes of death of patients with autoimmune hepatitis in Finland.
2. Find out the role of follow-up liver biopsies in patients' surveillance.
3. Study the non-invasive methods to quantify inflammation and fibrosis in autoimmune hepatitis.
4. Evaluate the prognosis of patients with autoimmune hepatitis after liver transplantation.

4 Patients and Methods

4.1 Patients

Study I. The first study comprised patients derived from The Social Insurance Institution of Finland (SII) database. The patients collected had been granted special reimbursement for autoimmune hepatitis medication and had either an International Classification of Diseases and Related Health Problems volume 10 (ICD-10) code K73.2 or K75.4 autoimmune hepatitis. This special reimbursement covers the costs of AIH medication for 70% of their original cost. Prior to approval, the certificate, written by a gastroenterologist or paediatrician, is checked by a medical examiner, pharmacist or a doctor at SII.

All citizens of Finland have a personal identity code (PIC). With PICs, we could identify the patients from hospital discharge registries (HILMO) as well as the Finnish Cancer Registry, which contains data of causes of death and population averages for survival and causes of death. The PIC key also allowed us to cross reference the data with Statistics Finland to see the time of birth and death to calculate survival. Statistics Finland also provided us five sex-matched controls with the same birth year, same age and living in Finland at the index date October 12th, 2016. The SII data from patients in the catchment area of Helsinki University Hospital was cross-checked with our own hospital's registry to validate the data, and all these patients fulfilled the Simplified criteria for diagnosis of autoimmune hepatitis¹⁵.

Patients were collected from 1995-2015, since we saw that ICD-10 (established in 1995) was more valid than previous classifications, including both chronic active hepatitis (K73.2), which AIH was previously called, as well as autoimmune hepatitis (K75.4). There have been no changes in the special reimbursement policy during this period.

Study II. In the histological follow-up study, the patient population consists of patients who have had a liver biopsy in Helsinki University Hospital during 1995-2012 with a diagnosis code of K73.2 or K75.4. In total, 193 patients had either K73.2 or K75.4. 123 of them fulfilled the 2008 Simplified criteria for the diagnosis of autoimmune hepatitis ¹⁵ for either probable or definite AIH. 20 patients were excluded due to a missing biopsy and three for positive viral hepatitis serology. Their diagnostic and follow-up biopsies were scored blindly by two experienced hepatopathologists. For inflammation and fibrosis, we used Metavir scoring ⁸⁸. Altogether, we reviewed 241 liver biopsies from 100 patients. Two patients were excluded at histological analysis because there were no AIH features in the second analysis. 66 patients had at least one follow-up biopsy.

We also had clinical, imaging and laboratory data from these patients. Remission was defined as the normalisation of immunoglobulin G and liver function test levels and the absence of interface inflammation in the liver biopsy.

Study III. In the study where we tried to evaluate non-invasive monitoring of AIH, we recruited twelve patients in Helsinki University Hospital (HUH) with confirmed AIH diagnosis according to Simplified diagnostic criteria for diagnosis of autoimmune hepatitis. Requirements included established AIH diagnosis and a planned liver biopsy for follow-up of AIH. We used liver biopsy as the gold standard, while patients subsequently underwent Fibroscan (Echosens, France) transient elastography, standard liver function tests including immunoglobulin G and ³¹phosphorus magnetic resonance spectroscopy (³¹P MRS). Biopsy, blood samples, transient elastography, and ³¹P MRS were performed within a one-month period, and before treatment was changed.

Study IV: Data for AIH prognosis after LT was gathered from the HUH Transplantation registry. HUH performs all liver transplantations in Finland. The first patient was transplanted due to AIH in 1992, and the data was collected until the end of 2012. We enrolled patients who fulfilled either probable or definite AIH diagnosis according to Simplified criteria for diagnosis of autoimmune hepatitis ¹⁵, resulting in 49 patients. Since we aimed to evaluate prognosis of AIH patients after LT, we included all these patients in the survival analysis. We have a biopsy surveillance protocol, and we take liver biopsies routinely at one and five years post-LT in AIH patients and every fifth year thereafter. Other primary endpoints were histological recurrence of AIH according to the Banff schema, and the effect of AIH recurrence on survival, and factors that contribute to AIH recurrence, fibrosis progression and cirrhosis development. We found 42 patients with follow-up (protocol) biopsies taken after the first year of LT. Histological samples were blindly evaluated by two hepatopathologists. Inflammation and fibrosis were graded according to the Metavir score ⁸⁸, and acute and chronic rejection were graded according to the Banff Schema ^{115,116}. AIH recurrence was diagnosed according to AIH diagnosis in a non-transplant setting, since there are no valid criteria for AIH recurrence after LT.

4.2 Statistics

Study I. The crude incidence and prevalence rates were calculated per 100,000 person-years. The sex- and age-specific numbers were calculated according to Statistics Finland data. Kaplan-Meier curves were used to show survival rates. Cox regression was used for survival hazard ratios.

The numbers of deaths and person-years at risk were counted by sex, age and years of follow-up. The expected numbers of all cause of death and for specific causes of death were calculated by multiplying the number of person-years in each stratum by the corresponding mortality rate in Finnish inhabitants. To calculate the standardised mortality ratio (SMR), the observed number of deaths was divided by the expected number. The 95% confidence intervals (CI) for the SMR assumed that the number of observed cases followed a Poisson distribution. Statistical computation was performed using the IBM SPSS Statistics version 24 and R environment for statistical computing and graphics (R Development Core Team 2015) using the popEpi package. $p < .05$ was considered as statistically significant.

Study II. In the biopsy follow-up, data was compared to primary data using Wilcoxon signed-ranks test for continuous parameters and McNemar's test for binary and ordinal data. Ordinal and linear regression models were used in a multivariate model to find data that correlated with fibrosis advancement or cirrhosis development. The inflammatory load was calculated during the follow-up period integrating the semi-quantitative score over time to obtain the area under curve. Cohen's kappa coefficient was used to calculate the correlation between histological and serological remission. SPSS v 22 (IBM corp, NY, USA), SAS (SAS institute, NC, USA) and Logexact v5 (Cytel corp, MA, USA) were used in statistical analysis.

Study III. The data from the biopsy, transient elastography, laboratory tests, and ^{31}P MRS were compared using the Pearson correlation coefficient for parametric tests and the Spearman rank correlation coefficient for nonparametric tests. A two-tailed T-test for unpaired samples was used to compare the means between groups. $p < .05$ was considered statistically significant. Statistical

analyses were performed with SPSS v 22 (IBM corp, NY, USA), SAS (SAS institute, NC, USA).

Study IV. In the AIH after LT article, two groups with nominal values were compared with the Chi-square test to find correlations. Patient and graft survival were calculated with Kaplan-Meier analysis. The log-rank test was used with immunosuppressive treatment and survival. Spearman's test was used between groups of patients with recurrent AIH and patients without. Cox regression was used in a univariate model to find risk factors for nominal parameters. All statistical analysis was done with the IBM SPSS version 22. $p < .05$ was considered as statistically significant.

4.3 Ethics

Approval for the study was obtained from the Ethics committee of Internal medicine, Helsinki University Hospital (diary number 150/13/03/01/2012) and the Internal Medicine department. According to Finnish regulations, patient consent is not needed in registry studies. Written informed consent for study III was retrieved from the study subjects.

5. Results

5.1 Study I. Epidemiology and causes of death

The mean incidence of AIH in Finland was 1.1/100,000/year, 1.6/100,000/year in women and 0.52/100,000/year in men between 2008-2015, Fig 3. Age and sex-specific incidences are shown in Figure 4. The prevalence of AIH in 2015 was 14.3/100,000, 23.0/100,000 in women and 6.6/100,000 in men. The overall survival was lower in AIH patients compared to controls. The standardised mortality ratio (SMR) was 1.81 (95% CI 1.47-2.20), $p < .001$, 1.69 (95% CI 1.32-2.14), $p < .001$ in women and 2.14 (95% CI 1.44-3.04), $p < .001$. SMR in age 0-29 years was 6.69 (95% CI 1.38-19.55), $p < .05$, between ages 30-59 SMR was 2.08 (95% CI 1.19-3.37), $p < .05$, and after 60 years SMR was 1.72 (95% CI 1.36-2.13), $p < .001$. Statistically significant causes for excess mortality in both sexes were hepatocellular carcinoma, cirrhosis, and autoimmune hepatitis. Diseases of the respiratory system as a cause of death were more common in women compared to the standard population, as were diseases of the circulatory system in men; However, not a single disease code was dominant in these disease groups.

Figure 3. Annual mean incidence of AIH in Finland, with permission, Study I

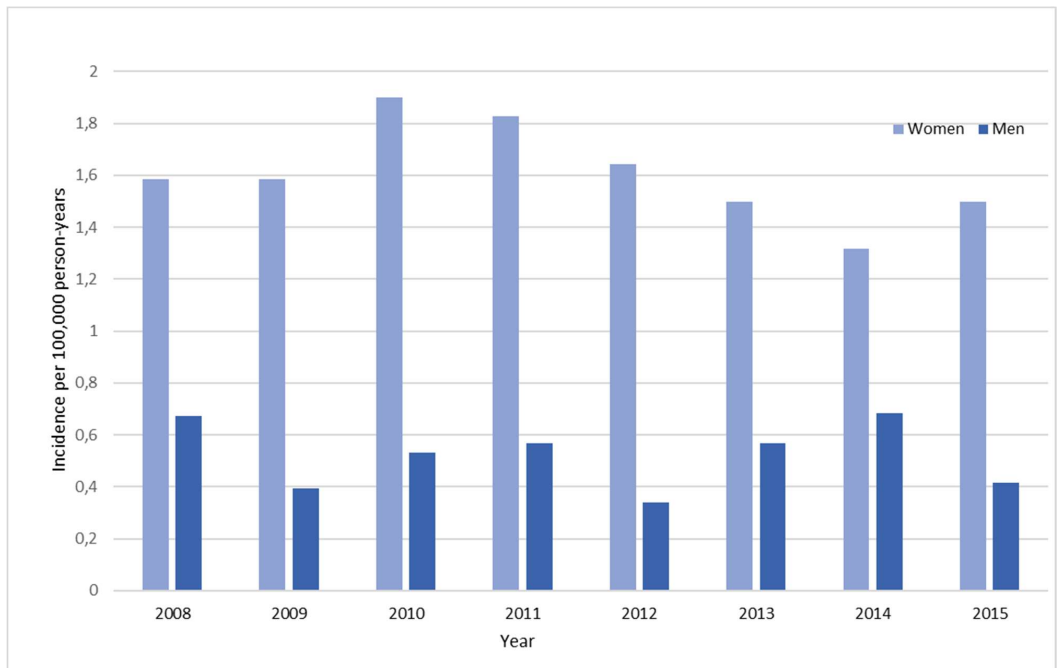
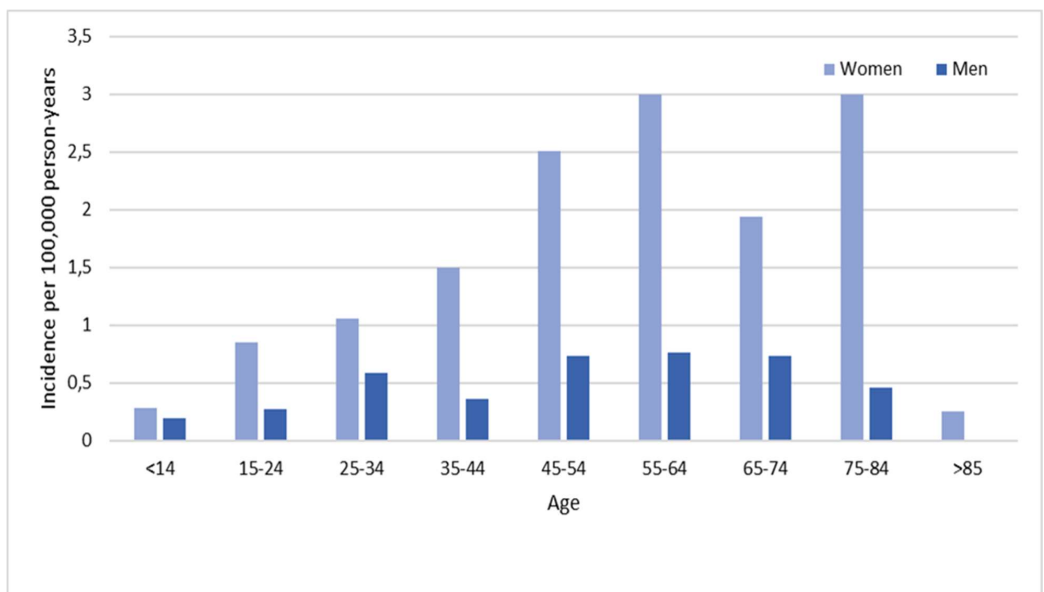


Figure 4. Age- and sex-specific incidence of AIH, with permission, Study I



5.2 Study II. Baseline and follow-up liver biopsies

At the time of diagnosis, only seven patients of 98 were cirrhotic (7.1 %), and 61 had no fibrosis at baseline. Of all the patients, 34 had additional features of cholangitis, either PBC or PSC. 52 patients presented with additional autoimmune disorders. During follow-up, 36 patients reached serological remission (normal transaminases and immunoglobulin G).

We had follow-up biopsies from 66 patients. Fibrosis progressed in 28 (42%), remained stable in 26 (39%) and resolved in 12 (18%). 29 (44%) were at histological remission at least once during follow-up. 9 patients (14%) developed cirrhosis. Surprisingly, serological and histological remission had only a poor correlation with kappa .171, $p=.003$.

Risk factors in an ordinal regression model at diagnosis for fibrosis progression were: in baseline liver biopsy, rosette formation odds ratio (OR) 2.0 (95% CI 1.1-7.1), $p=.027$, inflammation grade 1.7 (95% CI 1.7-1.8), $p=.047$, and necrosis 1.4 (95% CI 1.0-2.0), $p=.040$. Alkaline phosphatase (ALP) above the upper normal limit at baseline had an OR 10.1 (95% CI 1.5-66.9), $p=.020$. The absence of cholangitis had a protective effect with OR 0.40 (95% CI 0.1-1.0), $p=.044$.

During follow up, the cumulative ALP level had OR 24.0 (95% CI 2.7-214.6), $p=.005$ and cumulative inflammatory load (combined inflammation grade in follow-up biopsies) had OR 1.8 (95% CI 1.0-3.2), $p=.048$ for fibrosis progression. If inflammation in the biopsies was constantly grade two or more in the Metavir scale, the hazard ratio (HR) for development of cirrhosis was 5.1, (95 % CI 1.6-16.2), $p<.005$, and if interphase inflammation was constantly grade two or more, the HR was 6.1, (95 % CI 1.9-20.2), $p<.005$.

Patients with immunoglobulin G and alkaline phosphatase constantly over the upper normal limit (>15.0 and 105 , respectively) had HR of 6.4, (95 % CI 1.7-23.9), $p<.006$ for cirrhosis development.

Predictive factors for radiological or clinical cirrhosis development were calculated in a univariate model. Due to the low number of endpoints, it was not possible to construct multivariate analysis. Metavir fibrosis score of 3-4, $p=.0001$; cholestasis, $p=.007$; rosettes, $p=.044$; erythrocyte sedimentation rate, $p=.012$; albumin,

$p=.046$; and platelet count, $p=.003$ were the significant predicting parameters for cirrhosis development.

5.3 Study III. ³¹P Phosphorus Magnetic resonance spectroscopy in the follow up of AIH

Magnetic resonance spectroscopy seems to be a new promising non-invasive method for follow-up of both inflammation and fibrosis progression.

Phosphoenolpyruvate (PEP) correlated with the histological inflammation grade ($r=.746$, $p=.005$), and it separated patients with a Metavir grade 1-3 inflammation from grade 0 patients ($t=3.781$, $p=.009$). PEP levels >0.35 had a sensitivity of 100% (95% CI 54.1-100%), specificity of 66.7% (95% CI 22.3-96.7%), positive predictive value (PPV) of 75% (95%CI 34.9-96.8%) and negative predictive value (NPV) of 100% (95%CI 39.8-100%) to differentiate active inflammation (G1-3) from none, Fig 5.

The phosphomonoester to phosphodiester (PME/PDE) ratio and phosphoethanolamine to glyserophosphoethanolamine (PE/GPE) ratio correlated with the Metavir fibrosis score ($r=.668$, $p=.018$ and $r=.604$, $p=.037$, respectively. PE/PGE separated patients with Metavir 3-4 from Metavir 0-2 fibrosis ($t=3.810$, $p=.003$), Fig 6. Sensitivity of PE/GPE for differentiating fibrosis 3-4 from fibrosis 0-2 was 100% (95%CI 39.8-100%), specificity 50% (95%CI 15.7-84.3%), PPV 50% (95%CI 15.7-84.3) and NPV 100% (95%CI 39.8-100%) with 0.5 cut-off. With a cut-off of 0.7, the values were 50% (95%CI 6.8-93.2%), 100% (95%CI 63.1-100%), 100% (95%CI 15.8-100%) and 80% (95%CI 44.4-97.5%).

The median liver stiffness measured with transient elastography (TE) was 6.1 kilopascals, range 3.0-10.8. Compared to histology, TE overestimated fibrosis in four patients and underestimated in two. There was no statistical correlation with TE results and histological fibrosis, ³¹P MRS or laboratory results.

Figure 5. Phosphoenolpyruvate in three groups of inflammation. From **Study III**, reproduced with permission from Taylor & Francis ⁹². p-values added to original picture.

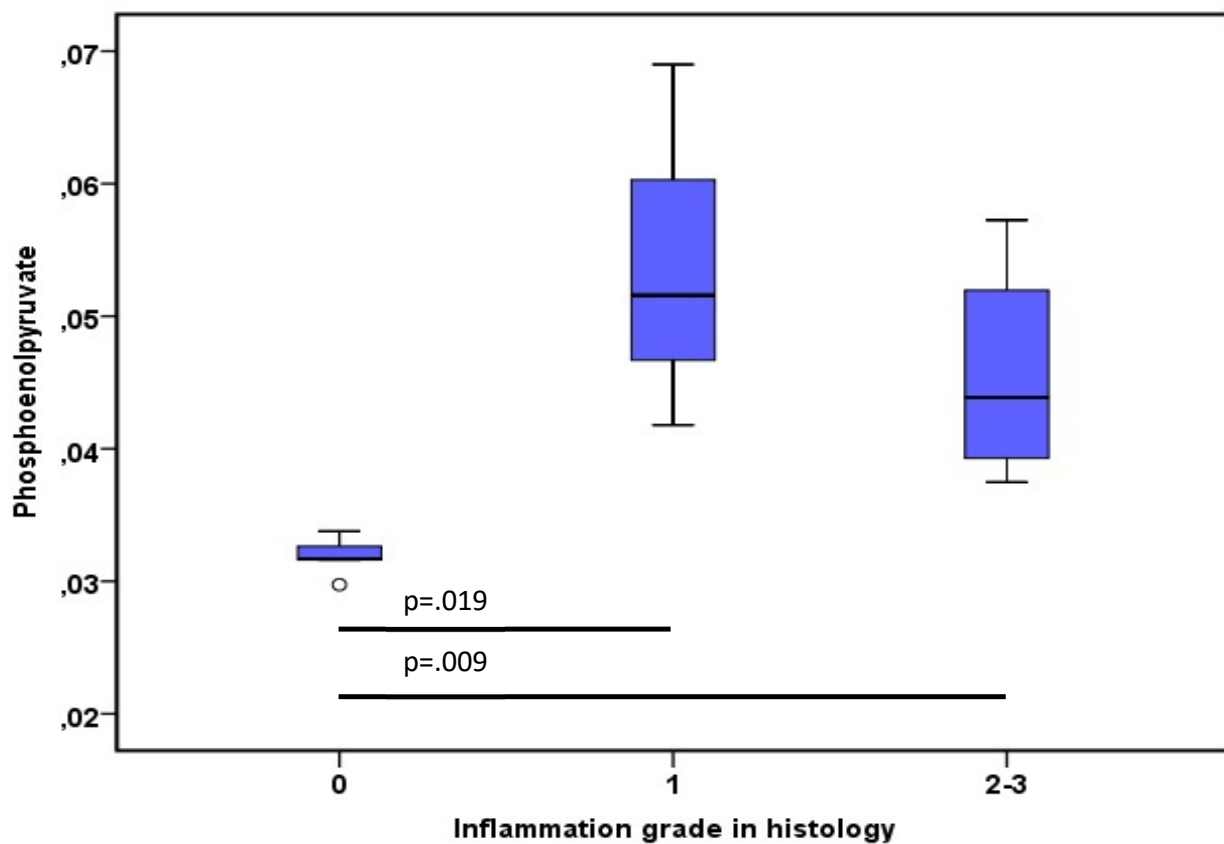
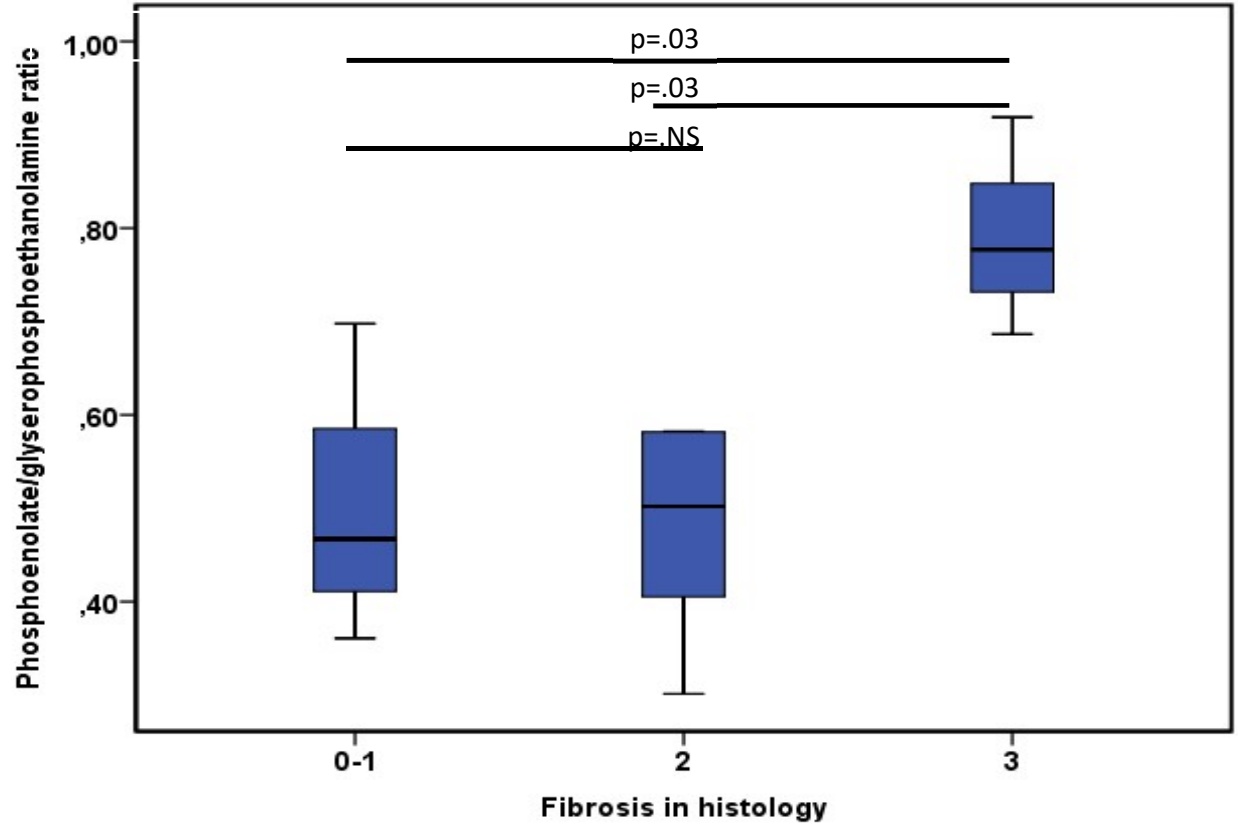


Figure 6. Phosphoenolate/glyserophosphoethanolamine ratio elevation is a sign of advanced fibrosis. From **Study III**, reproduced with permission from Taylor & Francis ⁹². p-values added to original picture.



5.4 Study IV. Prognosis of autoimmune hepatitis after liver transplantation

In the cohort of patients transplanted for AIH, follow-up or protocol biopsies were available from 42 patients. All patients were on low dose methylprednisolone, 60% on cyclosporine and 40% on tacrolimus. 69% had either azathioprine or mycophenolate. During a median of five-year (range 1.0-17.9) follow-up, AIH recurred in the graft in 15/72 (36% of patients), figure 7. The median time to recurrence of AIH was 2.7 years (range 1.0-15.1). One patient developed Metavir stage 3 fibrosis and one cirrhosis due to AIH recurrence, but no patients or grafts were lost due to recurrent AIH. LFTs were normal on 3 (20%) with histological AIH recurrence in a protocol biopsy. During follow-up, five grafts were lost (2 hepatic artery thromboses, primary graft dysfunction, biliary stricture formation, and vanishing bile duct syndrome). Three patients died (coronary artery disease, metastatic renal carcinoma, and metastasized hepatocellular carcinoma). None of the graft or patient losses were attributed to AIH recurrence.

Cyclosporine and tacrolimus were equal in this setting, but the absence of an antimetabolite increased the risk of AIH recurrence

Even though AIH recurrence had no impact on patient or graft survival, fibrosis progression was markedly accelerated in patients with AIH recurrence, Figure 8.

Figure 7. AIH recurrence over time after LT. From **Study IV**, reproduced with permission from Wiley publishing ²².

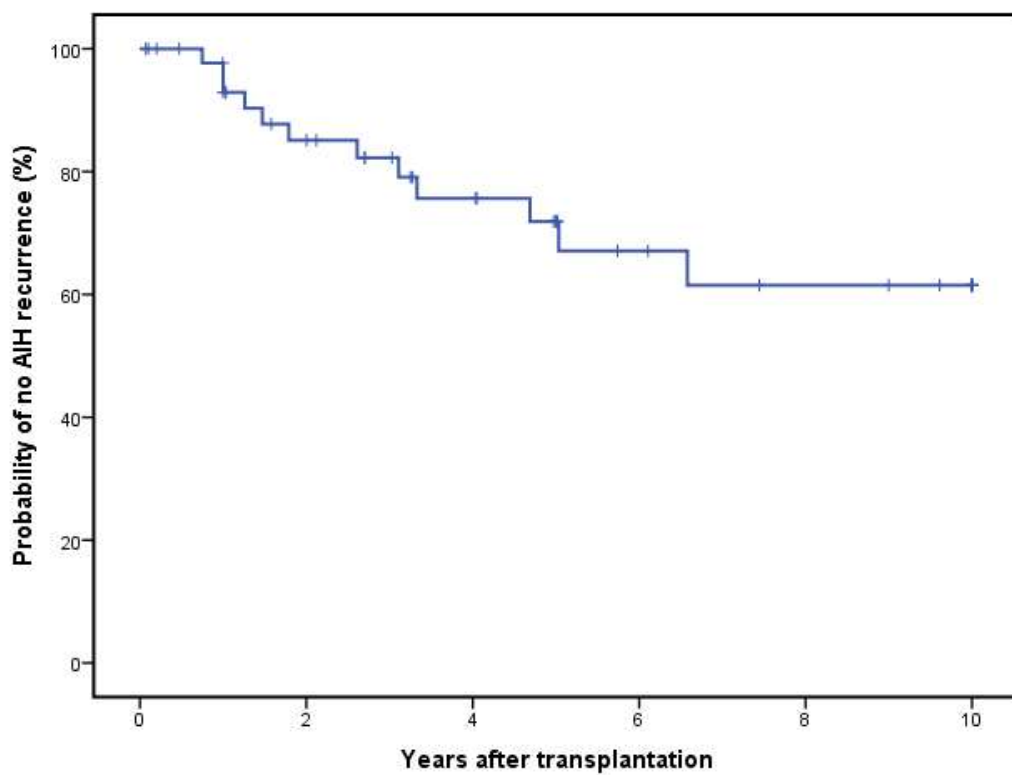
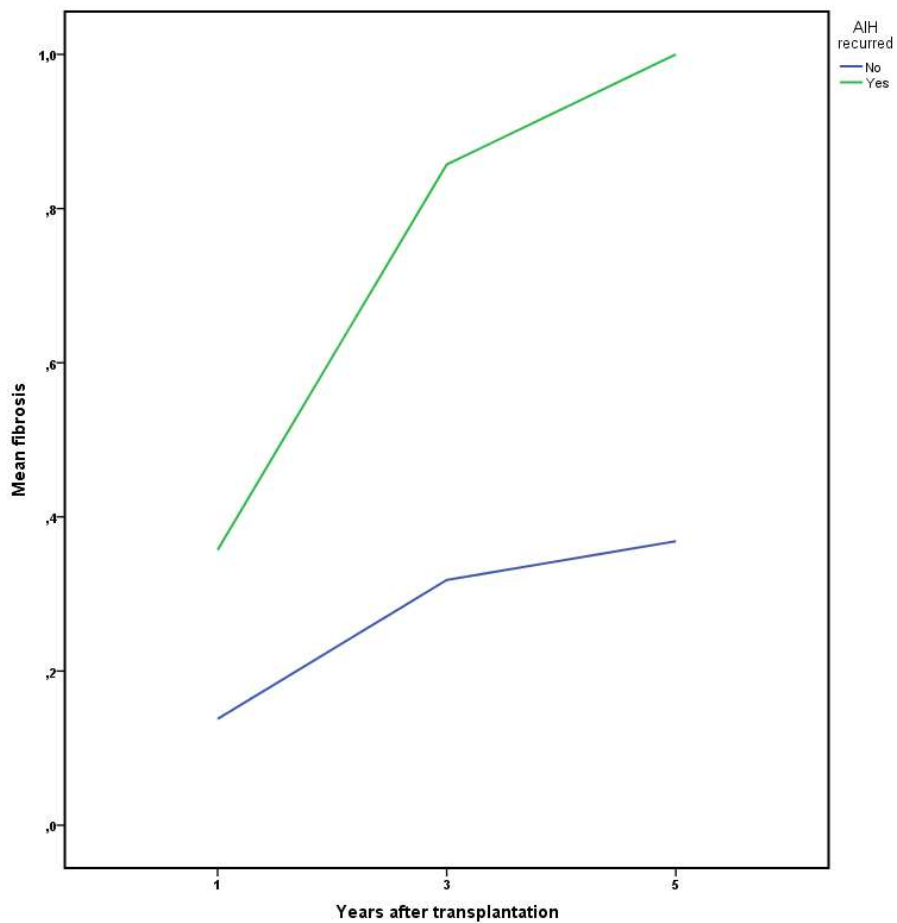


Figure 8. Progression of fibrosis according to AIH recurrence. From **Study IV**, reproduced with permission from Wiley publishing ²².



6 Discussion

While planning this manuscript, our primary goals were to report the epidemiological data of autoimmune hepatitis in Finland and evaluate different aspects of follow-up. We were able to assess incidence and prevalence of autoimmune hepatitis in Finland, as well as its impact on causes of death. We showed that histological and serological and inflammatory activity during follow-up impacts patients' outcome regarding fibrosis progression and cirrhosis development. Also, magnetic resonance imaging seems to be a promising method to evaluate fibrosis and inflammation non-invasively. Recurrence of autoimmune hepatitis was documented, as well as its impact on patient and graft survival.

6.1 Study I. Epidemiology and causes of death.

We showed in **Study I** that the incidence of AIH has remained stable in Finland since 2008 being 1.1/100,000/year. This is similar to what has been previously reported ^{7,23,24,27-30,33}. Female preponderance (76%), and prevalence of 14.3/100,000 were also parallel to previous studies. A new finding was that incidence among women rose with age, Figure 4. Previous studies have shown a bimodal distribution or a stable incidence by age. It is important to recognise that incidence in women was highest in the age group of 75-84, and new cases of AIH even emerged in women over 85 years old. In men, there were no AIH patients diagnosed after the age of 85 years, and no rise in incidence by age was seen. In both sexes, the greatest portion of patients were 45-84 years old. The mean ten-year survival was 84% and the twenty-year survival was 76 %. Survival was statistically significantly lower compared to controls. This highlights the importance of good quality of treatment and follow-up. Still, the survival of AIH patients in the present patients' cohort was markedly better than previously published, 48% at twenty years ⁸, although this data covered only patients followed up in one non-transplant centre. Data on long term prognosis of AIH is limited.

The cohort in **Study I** was distinctively different from what has previously been published, since registries have traditionally covered only one hospital area. So far, there has been only one nation-wide register study concerning AIH, the one published in Denmark ⁷. We had two registries where we could cross-validate the data, the hospital discharge registry and the Social insurance institution (SII) registry. The former probably overestimates the data since the diagnosis has not been re-checked. However, if a patient is recorded in the SII registry, the diagnosis must have been made by a gastroenterologist or a paediatrician, the patient must be on immunosuppressive medication, and personnel in the SII have checked that the diagnosis has been made properly. This setting does not require that valid scoring systems have been used in the diagnostics, so we do not know whether these patients fulfil international diagnostic criteria for AIH.

Causes of death registry maintained by Statistics in Finland

(https://www.stat.fi/til/ksyyt/index_en.html) and the Finnish cancer registry have data of all causes of death in Finland. We demonstrated that standardised mortality (SMR) was elevated in the total AIH population and in both sexes and all age groups. The most common causes of excess mortality were hepatocellular carcinoma (HCC), AIH per se, and liver cirrhosis. Respiratory system disorders in women and circulatory system diseases in men were statistically more prevalent in AIH patients than in controls, but the number of specific diagnoses within these groups were too small to be statistically analysed. It is important to recognise that the excess mortality in AIH is usually caused by AIH and its complications, and we did not see any additional mortality caused by immunosuppressive treatment (extrahepatic malignancies or infections). Even though HCC is less common in AIH cirrhosis than in other aetiologies of cirrhosis ^{7,83,117,118}, we should find prognostic markers or indices for HCC surveillance, since ultrasound follow-up in all cirrhotic AIH patients would not be cost-effective with annual incidence of 0.2%: It has been shown, that even an annual incidence of 4.1 of HCC would result in a cost of year saved of US\$112 993 ¹¹⁹.

We do not know whether doctors use revised 1999 or simplified 2008 criteria while writing the certificates but SII does not use these criteria. Most probably the certificates were written on more clinical grounds. It seems that most patients treated for AIH for a longer period indeed fill the diagnostic criteria since their

sensitivity is very good. We do not know whether liver biopsy was performed in all patients but supposedly prior to long term immunosuppressive treatment the biopsy has been taken in almost all if not from all patients. Also, we did not have data, whether patients had cirrhosis or not.

The main cause of excess mortality in AIH in a nation-wide registry was HCC. In **study II** we followed 98 patients from Helsinki university hospital. In this cohort we did not find a single HCC in AIH patients. Only 7% had cirrhosis at the time of diagnosis, which is presumably the reason that we were unable to find HCCs in our patient cohort. The frequency of cirrhosis was much lower than the traditionally referred 30% ^{7,27}, probably due to the well-functioning primary care system which makes it possible to find AIH patients already in their preclinical stage.

6.2 Study II. Role of the follow-up liver biopsies.

We showed that follow-up liver biopsies provide important prognostic information in the decision-making process, whether that patient is developing cirrhosis or advanced fibrosis. Not surprisingly, the cumulative inflammatory load was a significant risk factor. The most important histological parameters during follow-up were total inflammation and interphase inflammation with grade two or more.

To date, it is not clear what optimal strategy is to follow-up AIH patients. The current recommendation by AASLD and EASL is to aim to normalisation of transaminases and immunoglobulin G level ^{51,71}. The basis for this recommendation is that elevated liver function tests are associated to poor outcome, progression to cirrhosis, and relapse after treatment discontinuation ^{8,81,120,121}. On the other hand, these recommendations advise taking a liver biopsy prior to treatment discontinuation, but there is limited or no data to support this.

Liver biopsy is the gold standard for fibrosis and inflammation grading, but it has its limitations. It is usually safe, with a high success rate under ultrasound guidance and few complications ¹²². Even in the setting of specialized liver pathologist using a standardized and well-validated scoring system (Metavir) grading hepatitis c, there was a fair amount of disagreement when grading disease activity and necrosis between pathologists ¹²³. However, agreement between pathologist was almost perfect with fibrosis. One sample of liver tissue taken with a 1-2 cm needle with a 1.2-1.8 mm diameter represents 1/50 000 of the total mass of the liver and we now that fibrosis and inflammation are not equally distributed in the liver ¹²⁴.

As liver biopsy is invasive, we tried to calculate surrogate markers using only laboratory tests. Patients with immunoglobulin G and alkaline phosphatase constantly over the upper normal limit (>15.0 and 105, respectively) had HR of 6.4, (95 % CI 1.7-23.9), $p=.006$ for cirrhosis development. The number of patients developing cirrhosis was small (9 out of 98), which prohibited calculation of more complex models.

Fibrosis progressed in 28 patients (42%). Surprisingly, cumulative logarithmic alkaline phosphatase (ALP) had an odds ratio (OR) 24.0 (95% CI 2.7–214.6),

p = .005 for progression of fibrosis. Constantly elevated ALP had an OR of 3.4 (95 % CI 1.2-10.1), p=.026. We do not know why ALP would be a surrogate marker for fibrosis development: this is not explained by the concomitant AIH-PSC-overlap features. In fact, we saw that cholangitis or granulomas had a protective role against fibrosis development, though statistically insignificant. Pericholangitis had an OR of 0.4 (95%CI 0.1-1.0), p=.0435 for fibrosis progression. Furthermore, no patients with features of cholangitis developed cirrhosis in the follow-up. Age or gender did not influence fibrosis progression or cirrhosis development.

In total, 43.9% of patients were in histological remission at least at one time point during follow-up. It is not surprising that most patients had active inflammation, since most often liver biopsies have been taken due to clinical grounds, usually prior to treatment withdrawal or in case of inadequate treatment response. It seems that determining deep remission will also require liver biopsy in the future, since serological and histological remission demonstrated poor correlation with kappa .171, p = .003.

The weakness of the study was, that biopsies were not taken routinely. It is plausible that patient who were biopsied, had more complex AIH that required more data on histological activity. On the other hand, we usually take the biopsy prior to treatment with-drawl resulting in the high number of histological remissions in this cohort.

6.3 Study III. ³¹Phosphorus Magnetic resonance spectroscopy in the follow up of AIH.

Study III evaluated ³¹Phosphorus magnetic resonance spectroscopy in AIH patients' follow-up. This is the first time this method was used in this setting. Our study was a preliminary one of twelve non-cirrhotic patients with AIH showing promising results. Phosphoenolpyruvate (PEP), a link in hepatic gluconeogenesis, was elevated in patients with active inflammation. It is traditionally not linked to liver injury per se but seems to be a reliable surrogate marker of liver injury. It correlated with histological inflammation, and it was able to differentiate patients with active inflammation from patients in histological remission. To our knowledge, this finding is new regarding magnetic resonance spectroscopy and any liver disease.

The phosphomonoester (cell membrane precursor) to phosphodiester (cell membrane degradation product) ratio (PME/PDE) correlated well with fibrosis level, and the phosphoethanolamine (part of PME peak) to glyserophosphoethanolamine (part of PDE peak) ratio was able to separate patients with advanced fibrosis from patients with no or mild fibrosis. Our primary hypothesis was that transient elastography (Fibroscan®) would be a good indicator of liver fibrosis, but unexpectedly it seemed to have no role in fibrosis evaluation in our patient cohort, with overestimating fibrosis in two patients (probably due to active inflammation) but surprisingly underestimating fibrosis in four patients. We thought that evaluation of fibrosis would be secondary to inflammation, since treatment decisions are usually based on whether inflammation is suppressed or not, but we were able to find a method to evaluate both of these important parameters.

This study is promising, but the number of patients is so far too small to make definite assumptions on MRS. On the other hand, we are now more aware, which metabolic disturbances to expect in the spectroscopy of AIH patients.

6.4 Study IV. Prognosis of autoimmune hepatitis after liver transplantation

In patients transplanted for autoimmune hepatitis, we have used low dose methylprednisolone in combination with a calcineurin inhibitor in addition to an antimetabolite (azathioprine or mycophenolate mofetil) when well tolerated, which was the case in 69%. In our cohort, AIH recurred histologically in 36% of patients in a median of five-year (range 1.0-17.9) follow-up, but the disease course was benign, and no grafts were lost due to recurrent AIH, Fig 7. One patient developed vanishing bile duct syndrome, probably a form of chronic rejection, but no chronic rejections were diagnosed according to Banff schema ¹¹⁶. We used histological assessment since there is no consensus on AIH recurrence after LT concerning aminotransferase levels or immunoglobulin G levels.

The median time of AIH recurrence was 2.7 years from LT, but the range was 1.0-15.1 years. We also showed that AIH patients have a similar prognosis (patient and graft survival rates at one, five and ten years were 94, 86, and 86 % and 91, 77, and 74 %) after LT compared to other aetiologies. The five-year survival was also better than reported by the European Liver Transplantation Registry ¹⁰², 86 % vs 73%. One patient developed cirrhosis, and one had Metavir 3 fibrosis due to recurrent AIH. Development of cirrhosis was rare in our material (only one patient) and there was no statistical association found concerning it, but AIH recurrence correlated with the progression of fibrosis. Even though AIH seems to be benign, it is still important to follow-up and to try preventing the progression of fibrosis. Cyclosporine and tacrolimus were equal in this setting, but the absence of an antimetabolite increased the risk of AIH recurrence.

We have taken protocol biopsies in AIH patients at one year, five years and every five years thereafter after LT. The rationale for this is to try to find AIH recurrence and other significant liver disease at an early stage. It appeared that in three patients (20%) recurrent AIH was diagnosed while alanine and aspartate transaminases were within normal limits. We assume that finding patients with recurrent AIH at an earlier stage, gives us more time to adjust treatment prior to graft loss, even though we did not show that recurrent AIH has any effect on graft survival.

Previously, it has been shown that de novo or recurrent AIH after LT is more common in patients with AIH with features of PSC or PBC ^{125,126} than its pure form. Interestingly, in our material, features of cholangitis seemed to protect from AIH recurrence. This is still a difficult and complex subject since disease mechanisms and even diagnostic criteria within these diseases and their variant forms remain to be decided. Even though these are diseases, future studies are warranted for better understanding their disease mechanics and diagnostic methods.

The European liver transplant registry report from 2010 ¹⁰² raises concerns about AIH patients over the age of 50, and specifically their infection complications and excess infectious cause mortality. The overall five-year survival in AIH patients over fifty years old is only 61% after LT ¹⁰². In our cohort, one patient aged over fifty (out of 17) died of infectious complications in the post-operative period, showing that with proper patient selection, LT is safe for AIH patients aged over fifty.

We strongly recommend triple immunosuppression after LT due to AIH to prevent AIH recurrence. Our study shows that AIH recurrence is relatively common after LT but has very little impact on graft or patient survival at least in the median of 5-year follow-up.

7. Conclusions and future directions

The main findings and future questions are:

1. Prevalence of AIH has remained stable in the last years. Prevalence in a nation-wide cohort is comparable to previous reports from secondary and tertiary centres. Female preponderance is marked, and we show that especially in women, AIH occurs in all ages and often in the elderly. Hepatocellular carcinoma is rare but statistically the most important cause of excess death. Future studies are needed to recognise high-risk patients for hepatocellular cancer in order to target HCC surveillance in a cost-effective manner.
2. Liver biopsies might play a role in the follow-up of AIH, but to date, there are no good prognostic models to encompass liver histology therein. Ongoing histological inflammation is a risk factor for fibrosis progression and development of cirrhosis. Better non-invasive surrogate markers for disease progression and remission are needed as well as prognostic models and discussion concerning histological follow-up.
3. ³¹P magnetic resonance imaging of the liver is a promising follow-up tool and is acceptable to patients. These preliminary results should be confirmed in larger studies. Transient elastography was not useful in this setting.
4. AIH recurs after liver transplantation in 36% of patients, but its disease course is primarily benign. Triple immunosuppression (minimal dose corticosteroid, calcineurin inhibitor and antimetabolite) is advisable after LT when tolerable. We encourage protocol biopsies after LT due to autoimmune hepatitis liver diseases to find patients with recurrent AIH at an earlier stage.

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Acknowledgements

This study was conducted in the Helsinki University Hospital and Doctoral Programme in Clinical Research at the University of Helsinki. The study was financed by the Mary and Georg Ehrnrooth Foundation, the Instrumentarium Science Foundation, the Orion Research Foundation, and the Finnish Medical Foundation.

I am especially grateful for all the guidance and support that my supervisor professor Martti Färkkilä has given me. I respect his immense dedication to his work and immediate presence. His door was always open for questions and he responded to emails at any given time of day. I always received forward-looking advice and suggestions and he always had an answer ready. I also admire all that he has done for the culture and community of gastroenterologists and gastroenterology as a field of medicine and science.

I am very grateful to my other supervisor, docent Perttu Arkkila. I admire his dedication to his work and his ability to look at familiar things from different perspectives. His scientific experience and co-operation with different fields in medicine (human and veterinary), imaging, basic science, and surgery have opened my eyes to see research from variety of perspectives.

I want to thank the official reviewers, professor Tuomo Karttunen and professor Markku Voutilainen for their precious comments and advice.

Thank you, Luanne Siilasmaa, for editing the language of this dissertation.

Johanna Arola is the eminent force in hepatopathology in Helsinki and her advice was invaluable while planning and preparing my first two publications. Planning the histological follow up was pleasant with all those precise Excel files. I deeply appreciate all the hours that were spent looking at the histological samples and the fact that you arranged time for me when possible. It was delightful to see how an experienced and interested pathologist can see all those subtle clues between all the little cells under the microscope. I also thank Sonja Boyd for going through all those liver biopsies as well as providing information about the histological findings when writing the manuscripts.

I am grateful to professor Helena Isoniemi for all the help and knowledge regarding the field of liver transplantation. I appreciate the time you had for me to go through the files in the Transplantation Office between your night shifts. Professor Nina Lundbom and Antti Hakkarainen were a crucial part of the publication concerning the spectroscopy follow up and it was perceptive to see a different view to the liver. I also thank professor Eero Pukkala and Harri Mustonen, PhD, for introducing me to the world of statistics.

I thank all the colleagues in Meilahti net café, where truths are told and minor problems in all areas of life are discussed. I would like to give special thanks to Nina Barner-Rasmussen for going through the jungle of bureaucracy with the data on epidemiology and causes of death. Extra special thanks go to the people in the Malmi hospital a decade ago, where I got my spark in gastroenterology.

Finally, I am always grateful to my family: Niina, Otto, and Eino for being there, as well as my parents who have always supported me in achieving my life goals. Thank you.

Autoimmuunimaksatulehdus: Epidemiologia, ennuste ja seuranta

Autoimmuunimaksatulehdus on pitkäaikainen tulehduksellinen maksasairaus, jolle on tunnusomaista interfaasialueen maksasoluihin kohdistuva tulehdus koepalatutkimuksessa, koholla oleva veren kokonaisvasta-ainetaso ja verestä mitattavat ihmisen omaan elimistöön kohdistuvat vasta-aineet.

Autoimmuunimaksatulehduksen syy on useimmiten epäselvä, mutta yhdistelmä ympäristöriskeistä, puolustusjärjestelmän poikkeava tapa reagoida vieraisiin aineisiin ja perintötekijöistä johtuva elimistön puolustussolujen herkkyys reagoida maksan solujen proteiineihin. Tämä johtaa maksasolukuolemaan ja -tulehdukseen ja lopulta sidekudoksen muodostumiseen.

Autoimmuunimaksatulehduksen ilmaantuvuus ja esiintyvyys nousevat.

Osoitimme, että autoimmuunimaksatulehduksen mediaani ilmaantuvuus 1995-2005 oli 0,9/100 000/vuosi; 1,2/100 000/vuosi naisilla ja miehillä 0,38/100 000 /vuosi. Kasvua oli 0,28/100 000 - 1,04/100 000 tutkimusaikana. Esiintyvyys vuonna 2015 oli 14,3/100 000; 23,0/100 000 naisilla ja 6,6/100 000 miehillä. Standardoidun kuolleisuuden suhde oli muuta väestöä korkeampi kaikissa ikäryhmissä ja molemmilla sukupuolilla. Yleisimmät ylimääräisen kuolleisuuden syyt olivat maksasolusyöpä, maksakirroosi ja autoimmuunimaksatulehdus sinänsä.

Maksakudoksenäyte tarvitaan autoimmuunimaksatulehduksen alkuvaiheessa, jotta voidaan varmistaa diagnoosi, ja toisaalta koepalalöydöksillä tiedetään olevan ennusteellisia merkityksiä. Rutiininomainen kudoksenäyteseuranta sen sijaan on kiistanalainen. Helsingissä olemme ottaneet rutiininomaisesti seurantakoepaloja ja arvioimme niiden vaikutusta hoitovaihtoehtoihin ja ennusteeseen. Löysimme ennusteellisia muuttujia sidekudoslisän ja kirroosin kehittymiseen seurantakoepaloissa: interfaasialueen maksasoluihin kohdistuva tulehdus tai kokonaistulehdus, solutuho, sappikertymä tai rosetit alkuvaiheen koepalassa ennustivat sidekudoksen kehittymistä. Jos seurantakoepaloissa tulehdus oli jatkuvasti vähintään keskivaikea, kirroosin riskitiheys suhde oli 5.1 (95 % luottamusväli 1.6-16.2), $p < .005$ ja jos interfaasialueen maksasoluihin kohdistuva

tulehdus oli jatkuvasti vähintään kaksi, riskiteheyssuhde oli 6.1 (95 % luottamusväli 1.9-20.2), $p < 0,005$. Vain seitsemällä prosentilla potilaista oli kirroosi lähtötilanteessa. Sidekudosmäärä eteni 42 prosentilla potilaista, pysyi vakaana 39 prosentilla ja väheni 18 prosentilla.

HUS Kuvantamisessa on tutkittu magneettiresonanssispektroskopiaa 3 Teslan kuvantamislaitteella rasvamaksa- ja hepatiitti c -potilailla. Elastografia (Fibroscan®) on ultraäänipohjainen tekniikka, joka mittaa maksan jäykkyyttä, jonka ajatellaan liittyvän sidekudoksen määrään. Elastografia voi erottaa pitkälle edenneen sidekudoksen ja kirroosin normaalista maksasta. Se ei kuitenkaan mittaa tulehduksen määrää. Uusia kajoamattomia testejä tarvitaan tulehduksen ja sidekudoksen arvioinnissa, joten vertasimme maksan kudoksenäytettä, veriarvoja, elastografiaa ja magneettiresonanssispektroskopiaa toisiinsa.

Magneettiresonanssispektroskopia löysi erilaisen maksasolujen aineenvaihduntatuotteiden kirjon potilailla, joilla oli kehittynyt sidekudoslisä tai aktiivinen tulehdus verrattuna maksan Koepalaan. Elastografia ei toiminut sidekudoksen arvioinnissa verrattuna koepalalöydökseen.

Autoimmuunimaksatulehdus on vakiintunut maksansiirtoaihe, kun potilaalla on maksakirroosi, huono maksan toiminta, vaikeat maksasairauden oireet tai maksasolusyöpä. Helsingin yliopistollisessa sairaalassa on kattava rekisteri maksansiirron saaneista autoimmuunimaksatulehduspotilaista ja olemme keränneet säännölliset protokollakudoksenäytteet maksansiirron jälkeen. Vuosina 1982-2012 tehtiin 42 maksansiirtoa autoimmuunimaksatulehduksen takia.

Autoimmuunimaksatulehdus uusi 36%:lla potilaista siirron jälkeen ja keskimääräinen aika uusiutumiseen oli viisi vuotta (vaihteluväli 1,1-15,1). Uusiva autoimmuunimaksatulehdus ei vaikuttanut potilaan tai siirteen ennusteeseen. Potilaan ja siirteen ennuste oli 94% ja 86% yhden vuoden, 86% ja 91% viiden vuoden, ja 77% ja 74% kymmenen vuoden aikana. Hyljinnäestolääkitys kortisonin ja kalsiuneuriini-inhibiittorin yhdistelmä ilman atsatiopriinia tai mykofenolaattia lisäsi autoimmuunimaksatulehduksen uusiutumisen riskiä.

Autoimmun hepatit: Epidemiologi, prognos och uppföljning

Autoimmun hepatit är en kronisk inflammatorisk leversjukdom, som kännetecknas av interfask hepatit på histologisk undersökning, hypergammaglobulinemi och autoantikroppar mätt från blodet. Etiologi av autoimmun hepatit är mestadels oklar, men en triad av miljötriggers, misslyckande i immunförsvarets tolerans och känslighet på grund av genetiska faktorer inducerar en T-cellmedierad immunattack mot antigener i levern som leder till nekroinflammatorisk hepatocytiskada och fibros generation. Incidensen och prevalensen av AIH antas vara lika med det av primär biliar kolangit och dubbla mängden primär skleroserande kolangit. Epidemiologiska data av autoimmun hepatit är sällsynta, och samlas ofta in från ett enda centrum. Incidensen och prevalensen av autoimmun hepatit ökar. AIH åtföljs också ofta av andra autoimmuna sjukdomar. Vi visade att incidensen av median autoimmun hepatit mellan 1995 och 2015 var 0,9/100 000/år, 1,2/100 000/år hos kvinnor och 0,38/100 000/år hos män, och den gick från 0,28/100 000 till 1,04/100 000 under studieperioden. År 2015 var förekomsten av autoimmun hepatit 14,3/100 000, 23,0/100 000 hos kvinnor och 6,6/100 000 hos män. Det standardiserade dödlighetstalet ökade i alla åldersgrupper och i båda könen. De mest vanligast förekommande orsakerna till dödlighet jämfört med standardpopulationen var levercancer, cirros och autoimmun hepatit i sig.

Leverhistologi behövs vid autoimmun hepatit diagnos för att fastställa diagnos, och histologiska fynd är kända för att vara av prognostisk betydelse. Implikationen av rutinmässig uppföljning med biopsier är mer kontroversiell. I Helsingfors har vi rutinmässigt tagit leverbiopsiprover och bedömt deras inverkan på behandling och prognos. Vi kunde utvärdera prognostiska variabler för att främja fibros eller cirros genom att följa upp biopsierna: Interfas eller total inflammation, nekros, kolestas eller rosettbildning vid baslinjebiopsi. Om inflammationen vid uppföljningen av biopsierna ständigt var grad två eller mer på en METAVIR-skala, var riskförhållandet för cirros 5.1 (95 % konfidensintervall 1.6-16.2), $p < .005$, och om interfask inflammation var konstant grad två eller mer, var riskförhållandet 6.1 (95 % konfidensintervall 1.9-20.2), $p < .005$. Endast sju procent av patienterna var

cirrotiska vid baslinjen. Fibrosis fortskred hos 42 % av patienterna, förblev stabil hos 39 % och minskade hos 18 %.

Vid Helsingfors universitetssjukhus Bilddiagnostik har dessutom magnetresonans-spektroskopi med 3 Tesla modalitet använts vid icke-alkoholhaltiga fettlever och hepatit C. Elastografi (Fibroscan®) är en ultraljudsbaserad teknik som bedömer fibros vid leversjukdom. Elastografi kan särskilja avancerad fibros och cirros från normal leverhistologi men är inte användbart vid lindrig fibros. Dessutom spelar det ingen roll vid utvärderingen av inflammation. Nya icke-invasiva tester vid utvärdering av inflammation och fibros behövs, och vi jämförde leverhistologi med leverfunktionstest, elastografi och magnetisk resonansspektroskopi. Magnetisk resonansspektroskopi visade olika nyckeltal för utvalda hepatocytförändringar i metaboliter hos patienter med avancerad fibros eller aktiv inflammation hos tolv på varandra följande autoimmuna hepatitpatienter jämfört med leverhistologi. Elastografi var verkningslös vid kvantifiering av fibros.

Autoimmun hepatit är en väl etablerad indikation för levertransplantation hos cirrotiska patienter med obehandlade symtom på portal hypertoni, dålig leverfunktion, allmänna symtom eller levercancer. Vid Helsingfors universitetssjukhus har vi ett omfattande register över levertransplanterade AIH-patienter och vi har regelbundet fört protokoll över biopsier efter transplantation. Under åren 1982–2012 gjordes 42 levertransplantationer på grund av autoimmun hepatit. Autoimmun hepatit recidiverade hos 36 % av patienterna och mediantiden till recidiv var fem år (intervall 1.1–15.1). Recidiv autoimmun hepatit påverkade inte patientens eller transplantationens överlevnad. Patientens och transplantationens prognos var 94 % och 86 % efter ett år, 86 % och 91 % efter fem år, och 77 % och 74 % efter tio år. Immunosuppression utan en antimetabolit ökade risken för autoimmun hepatit recidiv.